

Recommendations for Use: Peginterferon alfa and ribavirin in combination with Direct Acting Antivirals (DAA) Boceprevir or Telaprevir

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VHA Pharmacy Benefits Management Services, the Medical Advisory Panel, VISN Pharmacist Executives,
Office of Public Health and Hepatitis C Resource Centers

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

Introduction:

In May 2011, the FDA approved two direct acting antivirals (DAA's - also referred as oral HCV protease inhibitors), boceprevir and telaprevir. Both of these agents are indicated for treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin in adult patients with compensated liver disease including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

Place in therapy of peginterferon/ribavirin with boceprevir or telaprevir

- Peginterferon and ribavirin in combination with boceprevir or telaprevir have demonstrated superior efficacy to peginterferon/ribavirin in the treatment of chronic hepatitis C in **genotype 1** patients who were either treatment-naïve or treatment-experienced.
- Boceprevir or telaprevir **must not be used as monotherapy**; therefore, patients must be able to tolerate peginterferon/ribavirin for combination with boceprevir or telaprevir.
- For patients who experience intolerance to either boceprevir or telaprevir, patients may be switched to the other oral hepatitis C protease inhibitor if clinically appropriate. For patients who experience virologic failure to boceprevir- or telaprevir-containing regimens, patients should **not be switched** to the other oral hepatitis C protease inhibitor due to concerns of presumed cross resistance.

Patient Selection

- The HCV Clinical Case Registry (CCR) Direct Acting Antiviral (DAA) report indicates that approximately 85,000 HCV viremic genotype 1 Veterans received care in 2010 (<http://vaww.hepatitis.va.gov/data-reports/ccr2010/DAA-EligibleCurlnCare-Jan11-HCVVirGT1-CCRALD-2010-All.asp>). VISN and facility level data are also available which can be used to identify the number of potentially eligible patients at your facility. The CCR software is deployed throughout the VHA and provides a local registry at every VHA facility to support local care delivery and to help sites further assess patient-level data. Each facility has a CCR IT contact that can provide you access to your local CCR (http://vaww.publichealth.va.gov/docs/quality/CCR_IT_Contacts.pdf) and a designated CCR coordinator who manages pending patients and may serve as a useful local resource (http://vaww.publichealth.va.gov/docs/quality/CCR_Hep_C_Coordinators.pdf).
- Of the 165,000 HCV viremic Veterans in VHA care in 2010, only 22% have previously received Hepatitis C therapy. It is estimated that approximately 30-50% of HCV viremic Veterans may have contraindications to HCV therapy and therefore are not treatment candidates. Because HCV protease inhibitors must be used in combination with peginterferon/ribavirin, any patient with a contraindication to peginterferon/ribavirin would also not be eligible to receive a boceprevir- or telaprevir-containing regimen.
- Due to the complexities of the DAA regimens including response guided therapy, high pill burdens, food requirements, adverse events, and potential drug interactions the provider must discuss the potential risks versus benefits of HCV therapy and a shared decision with the patient should be made. Chronic HCV-infected patients with minimal fibrosis (METAVIR stage 0, 1 based on an adequate liver biopsy specimen) are at lower risk for developing advanced liver disease in the short-term. Minimal fibrosis cannot be assumed in the absence of a liver biopsy or an inadequate biopsy specimen. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation without treatment with the understanding that treatment should be reconsidered if liver disease progresses. For a more complete listing of pre-treatment considerations, refer to the *VA HCRC and HCV Program Office Treatment Recommendations* and the *AASLD Practice Guidelines*.
- Patients who failed to respond virologically to treatment had a high likelihood of developing resistance: resistant variants were observed in over 80% of subjects who did not achieve an SVR.
- It is expected that several new HCV agents, including potential interferon-free regimens, will be available in the next 1 to 5 years. Depending on the stage of liver disease and other patient characteristics and given the

potency and potential convenience of these investigational regimens some patients and providers may decide to delay treatment until these new regimens are FDA approved.

	Peginterferon alfa and ribavirin with boceprevir	Peginterferon alfa and ribavirin with telaprevir
Contraindications to Hepatitis C Therapy		
Characteristics of Persons for Whom Therapy is Contraindicated	VA HCRC and HCV Program Office Treatment Recommendations: <ul style="list-style-type: none">• Major uncontrolled depressive illness• Solid organ transplant (renal, heart, or lung)• Autoimmune hepatitis or other autoimmune conditions known to be exacerbated by PEG IFN/RBV• Untreated thyroid disease• Pregnant or unwilling to comply with contraception (Ribavirin is Category X)• Severe concurrent medical disease (e.g., end stage AIDS, significant CAD, cancer)• Age < 2 years• Known hypersensitivity to drugs used to treat HCV Others contraindications listed in prescribing information (vary based upon preparation): <ul style="list-style-type: none">• Decompensated liver disease;• Hemoglobinopathies (e.g., thalassemia major, sickle cell disease);• Coadministration with didanosine	
Contraindications to boceprevir or telaprevir (not listed above)	<ul style="list-style-type: none">• Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events (e.g, ergot derivatives, lovastatin, simvastatin, triazolam);• Potent CYP3A4/5 inducers where significantly reduced HCV PI plasma concentrations may be associated with reduced efficacy (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, St. John’s Wort).	
Warnings/Precautions to Hepatitis C Therapy		
Warning/Precautions with peginterferon and ribavirin (vary based upon specific preparation)	<ul style="list-style-type: none">• Birth defects and fetal death; therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Use 2 or more forms of contraception for at least 6 months after treatment has concluded and monthly pregnancy tests• Hemolytic anemia; may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions• History of significant or unstable cardiac disease• Risk of hepatic failure and death; monitor hepatic function during treatment and discontinue treatment for hepatic decompensation• Hypersensitivity and serious skin reactions including Stevens-Johnson Syndrome• Pulmonary disorders• Neuropsychiatric events• Infections• Colitis and pancreatitis• Bone marrow suppression• Ophthalmologic disorders• Cerebrovascular disorders• Autoimmune and endocrine disorders• Retinopathy• Dental/periodontal disorders	
Warning/Precautions with boceprevir or telaprevir	<ul style="list-style-type: none">• Pregnancy• Anemia• Neutropenia	<ul style="list-style-type: none">• Pregnancy• Serious skin reactions• Rash• Anemia
Adherence Assessment to Hepatitis C Therapy		
Adherence Assessment	Document ongoing nonadherence to prior medications, medical treatment or failure to complete HCV disease evaluation appointments and procedures.	

	The ability to self-administer or to arrange appropriate administration of parenteral medication as well as, refrigerator for storage of peginterferon	
Treatment Considerations for boceprevir and telaprevir	<p>Boceprevir pill burden: 12 per day (4 pills every 8 hours) with food</p> <p>Length of <i>boceprevir component</i> of regimen: 24, 32, or 44 weeks, depending on virologic response and prior treatment history</p> <p>Total length of therapy (including peginterferon/ribavirin): 28, 36, or 48 weeks</p> <p>4-week peginterferon/ribavirin lead-in phase required per FDA labeling: Assess tolerance, adherence, and interferon responsiveness to peginterferon/ribavirin at week 4 before deciding to embark upon boceprevir/peginterferon/ribavirin-containing regimen.</p>	<p>Telaprevir pill burden: 6 per day (2 pills every 8 hours) with food containing at least 20g of fat</p> <p>Length of <i>telaprevir component</i> of regimen: 12 weeks regardless of prior treatment history</p> <p>Total length of therapy (including peginterferon/ribavirin): 24 or 48 weeks</p> <p>Lead-in phase not required per FDA labeling; Lead-in treatment for 4 weeks with peginterferon/ribavirin in a prior treatment failure population did not improve SVR rates or affect frequency of emergence of resistant strains over a simultaneous start.</p>
Considerations for Treatment Naïve- and -Experienced Patients		
IL-28B Testing (A human genetic variation previously shown to predict hepatitis C prognosis and response to therapy in people with HCV)	Although not included as part of the original protocols, effect of IL28B on treatment response was retrospectively evaluated. In treatment-naïve subjects with the C/T and T/T genotypes, boceprevir-containing regimens resulted in significantly higher SVR rates than PEG/riba alone ($p=0.005$), whereas SVR rates did not differ significantly between the boceprevir-containing arms and PEG/riba alone in the C/C genotype subgroup. Virologic responses to boceprevir occurred more rapidly in subjects with the C/C genotype relative to PEG/riba; over 96% of C/C subjects treated with boceprevir had undetectable HCV-RNA by week 8, whereas similar response rates were not achieved until week 24 for those treated with PEG/riba. In treatment-failure subjects, IL28B genotype effects were less pronounced and did not differ significantly based on IL28B genotype ($P=0.60$). These results should be interpreted with caution.	Although not included as part of the original protocols, IL28B genotype was retrospectively determined in subsets of two Phase 2 trials and two Phase 3 trials. Samples from 42% (454/1088) of treatment-naïve patients were available and samples from 80% (527/662) of treatment-experienced subjects were available. Of note, the substudy population included very few African American subjects. In both treatment-naïve and -experienced subjects, those with the C/C, C/T and T/T genotypes all had higher SVR rates with telaprevir-containing regimens than peginterferon and ribavirin alone. These results should be interpreted with caution because the sample size of some subgroups was small, results were obtained retrospectively, and the cohort may not fully represent the study population.
Null Responders (defined as decrease of $<2 \log_{10}$ in HCV viral load after 12 weeks of prior HCV therapy with peginterferon/ribavirin)	Boceprevir was not initially studied in null responders; this population was excluded from the Phase 2/3 study of patients who had previously failed treatment. Subsequently, patients who were in the PEG/riba control arms of either SPRINT-2 (naïve) or RESPOND-2 (experienced) who did not achieve SVR were eligible to enroll in the PROVIDE study. PROVIDE examined the efficacy of BOC + PR in the 52 patients who were PEG/riba null	Telaprevir was specifically studied in null responders and demonstrated superior efficacy compared to peginterferon/ribavirin therapy alone. In null responders, SVR rates were 29% (21/72) in the T12PR48 group, 33% (25/75) in the lead-in T12PR48 group, and 5% (2/37) in the PEG/riba group.

	<p>responders in the previous studies. Following a null response to prior PEG/riba therapy, 38% (20/52) achieved SVR with boceprevir + PEG/riba (25% of black patients, 46% of non-black patients.)</p>	
Use in Special Populations		
Cirrhotics	<p>Clinical trials for both telaprevir and boceprevir included patients with cirrhosis. Both naïve studies for each drug had very few cirrhotic patients in each arm and patients were categorized slightly different (F4 vs F3/F4). More cirrhotic patients were included in the telaprevir treatment experienced trial than the boceprevir trial, (26% vs 14%, respectively). However, the overall numbers are small and no statistical significance could be assessed for any of these trials. Use caution when trying to make any meaningful conclusion from such small subpopulations.</p> <p>In the telaprevir study of naïve pts with F4 cirrhosis, response rates in the 21 cirrhotic patients was 62% vs 33% (7/21) with peginterferon/riba. In the treatment experienced patients with F4 response rates were 84% (54/64), 44% (11/25), and 28% (12/43) vs 13%(7/30), 10% (1/10), and 5% (1/19) in peg/riba groups depending on their prior treatment history (relapsers, partial, or null responders, respectively).</p> <p>In boceprevir naïve study, response rates were 42% in the 24 patients in boceprevir arms with F4 cirrhosis. In those with either F3 or F4 in the boceprevir 44 week group response rates were 52% (22/42) vs 38% (9/24) in those treated with peg/riba. In treatment-experienced patients, the SVR rates in the cirrhotic F4 patients receiving boceprevir for 44 weeks were 77%(17/22) vs. 0% (0/10) in the peginterferon/ribavirin group; in those with either F3 or F4 in the boceprevir 44 week group response rates were 68% (21/31) vs 13% (2/15) in the peg/riba group. Null responders were not included.</p>	
African Americans	<p>Overall, the number of African American patients in each of clinical trials for boceprevir and telaprevir were small; however, more African American patients were included in boceprevir clinical trials compared to telaprevir trials.</p> <p>Fourteen percent of treatment naïve and 12% of treatment experienced patients receiving boceprevir were black. In the treatment naïve SPRINT-2 study for boceprevir, the SVR rate in African American subjects was 42%-53% versus 23% in those treated with peg/riba. In treatment experienced African American patients, the SVR rates were 58%-68% in boceprevir treated patients versus 24% in patients treated with peginterferon/ribavirin.</p> <p>Only 9% of treatment naïve and 4% of treatment experienced patients receiving telaprevir were black. In the treatment naïve ADVANCE study for telaprevir, the SVR rate in African American subjects was 62% (16/26). In treatment experienced African American patients, the SVR rate was 63% (12/19). Use caution when trying to make any meaningful conclusion from such small numbers.</p>	
For women of childbearing potential (this applies to female patients or in female partners of male patients)	<p>Because HCV protease inhibitors must be used in combination with ribavirin therapy (which is pregnancy category X), it should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Systemic oral contraceptives may not be effective in women taking boceprevir or telaprevir; therefore, it is recommended that two non-hormonal methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with boceprevir or telaprevir and concomitant ribavirin and for at least 6 months after treatment has concluded.</p>	
Co-Infection with HIV	<p>Patients co-infected with HIV/HCV were excluded from the pivotal clinical trials with boceprevir and telaprevir; limited efficacy and safety data are available in this population, which have been presented in abstract form. There are potentially clinically significant drug interactions with certain antiretrovirals which may require avoidance of certain drug combinations or specific dose modifications. Treatment with co-infected HIV/HCV individuals should only be considered if co-managed by an experienced HIV provider. These decisions must be adjudicated at the local facility.</p>	

	In February 2012, the manufacturer of boceprevir issued a statement that they do not recommend the coadministration of boceprevir and ritonavir-boosted HIV protease inhibitors . A pharmacokinetic study evaluated drug interactions between boceprevir and ritonavir-boosted human HIV protease inhibitors in healthy volunteers (n=39). In the study, concomitant administration of boceprevir with ritonavir boosted atazanavir, darunavir, or with lopinavir/ritonavir resulted in reduced exposures of the HIV protease inhibitors and boceprevir. Boceprevir reduced mean trough concentrations of ritonavir-boosted atazanavir, lopinavir, and darunavir by 49%, 43% and 59%, respectively. Mean reductions of 34 to 44 percent and 25 to 36 percent were observed in AUC and Cmax of atazanavir, lopinavir, and darunavir. Co-administration of ritonavir-boosted atazanavir with boceprevir did not alter the AUC of boceprevir, but co-administration of boceprevir with lopinavir/ritonavir or ritonavir-boosted darunavir decreased the AUC of boceprevir by 45% and 32%, respectively.	
Co-Infection with Hepatitis B	Patients co-infected with HIV/HBV were excluded from the pivotal clinical trials with boceprevir and telaprevir; therefore, efficacy and safety data are not available in this population. Pharmacokinetic studies demonstrate concomitant administration of tenofovir and telaprevir resulted in similar telaprevir exposure but higher tenofovir exposure. Telaprevir prescribing information recommends that increased clinical and laboratory monitoring are warranted and tenofovir should be discontinued in patients who develop tenofovir-associated toxicities.	
Liver Transplant	Patients with recurrent post-transplant HCV infection were excluded from the pivotal clinical trials with boceprevir and telaprevir; therefore, efficacy and safety data are not available in this population. There are potentially clinically significant drug interactions with certain immunosuppressants which may require critical evaluation and dose modifications to the transplant regimen. Treatment of patients with recurrent post-transplant HCV infection should only be considered if co-managed by an experienced transplant provider. These decisions must be adjudicated at the local facility.	
Solid Organ Transplant (other than liver):	Patients with solid organ transplant were excluded from the pivotal clinical trials with boceprevir and telaprevir; therefore, efficacy and safety data are not available in this population. There are potentially clinically significant drug interactions with certain immunosuppressants which may require critical evaluation and dose modifications to the transplant regimen.	
Substance or Alcohol Use	Patients with a history of substance or alcohol use who are abstinent should be considered for treatment. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV anti-viral treatment. Patients with active substance or alcohol use disorder who are willing to participate in a substance use program should be considered for therapy on case-by- case basis.	
Renal Impairment		
Peginterferon alfa	<ul style="list-style-type: none">• Peginterferon alfa-2a: In patients with CrCl <30 ml/min and end-stage renal disease requiring hemodialysis, peginterferon alfa-2a should be reduced to 135mcg once weekly and signs/symptoms of interferon toxicity should be closely monitored.• Peginterferon alfa-2b: For patients with CrCl between 30-50 ml/min dose reduce by 25%; for CrCl between 10-29ml/min including those on hemodialysis dose reduce by 50%. Monitor for signs/symptoms of interferon toxicity.	
Ribavirin	Prescribing information depends on ribavirin product being used. Most generic products indicate that ribavirin should not be administered to patients with creatinine clearance <50 mL/min. Copegus prescribing information states that for CrCl between 30-50ml/min alternate 200mg and 400mg every other day. For CrCl <30ml/min use 200mg daily.	
Oral Hepatitis C Protease Inhibitors	Boceprevir: No dosage adjustment is necessary for patients with any degree of renal impairment.	Telaprevir: No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment; telaprevir was not studied in patients with end-stage renal disease or hemodialysis. Telaprevir exhibits non-linear and time-dependent pharmacokinetics, hence exposure to telaprevir may be greater in renally impaired patients following multiple-dosing.

		Further studies are underway to investigate.
Hepatic Impairment		
Peginterferon alfa	Use with caution in patients with cirrhosis as they may be at risk of hepatic decompensation when treated with alfa interferons. Monitor closely.	
Ribavirin	Copegus: not evaluated; clinical trials restricted to patients with Child-Pugh Class A disease; not recommended for patients with decompensated disease.	
Oral Hepatitis C Protease Inhibitors	Boceprevir: No dose adjustment is required for patients with mild, moderate or severe hepatic impairment. However, the safety and efficacy of boceprevir have not been studied in patients with decompensated cirrhosis (defined as Child-Pugh Class B or C, score ≥ 7).	Telaprevir exposure is reduced by 53% in patients with Child-Pugh B hepatic impairment; telaprevir should not be administered to patients with moderate to severe hepatic impairment (Child-Pugh Class B or C, score ≥ 7).

Initiating and Managing Therapy in Treatment Candidates

The following table provides guidance on monitoring of therapy.

Lab Assays for HCV RNA Assessments: At individual facilities, a sensitive HCV RNA assay with a lower limit of quantitation or detection cut-off should be used for decision making to determine treatment duration with response guided therapy. The FDA recommends using HCV RNA assays that have a lower limit of quantification of <25 IU/mL and a limit detection of 10-15 IU/mL. For the purpose of assessing response-guided therapy eligibility, HCV RNA values <25 IU/mL were considered to be undetectable.

Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	6 Mo Post
CBC w/diff ALT/AST Total Bili Albumin PT/INR TSH Cr Electrolytes Glucose HBA1c in Diabetics Uric acid (telaprevir) Pregnancy test in women of child- bearing age Serum ferritin, iron panel ANA Depression Screening Psychiatric and SUD screening HCV RNA HCV genotype HIV test Liver biopsy Eye exam for	CBC w/diff ALT/AST Uric acid (telaprevir) Uric acid (telaprevir) Total Bili (telaprevir) Adherence assessment	CBC w/diff ALT/AST Uric acid (telaprevir) Total Bili (telaprevir) HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment	CBC w/diff ALT/AST Uric acid (telaprevir) Total Bili (telaprevir) HCV RNA Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST Cr TSH Glucose Uric acid (telaprevir) Total Bili (telaprevir) HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment	CBC w/diff ALT/AST Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST Total Bili Albumin PT/INR TSH Cr Electrolytes Glucose HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment Assess for drug interactions Adherence assessment	CBC w/diff ALT/AST Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST TSH Glucose HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment	CBC w/diff ALT/AST TSH Glucose HCV RNA Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST Pregnancy test in women of child- bearing age Depression Screening Adherence assessment	CBC w/diff ALT/AST Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment Assess for drug interactions	CBC w/diff ALT/AST Total Bili Albumin PT/INR TSH Cr Electrolytes Glucose HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment	CBC w/diff ALT/AST Total Bili Albumin PT/INR TSH Cr Electrolytes Glucose HCV RNA Pregnancy test in women of child- bearing age Depression Screening Eye exam for retinopathy in those with diabetes or hypertension Adherence assessment

those patients with diabetes or hypertension														
HBsAg														
HBsAb														
Anti Hep B														
Core(total)														
HAV Ab(total)														
Assess for drug interactions														

Resistance

Careful virologic monitoring is required to assess when treatment is futile and should be halted to avoid the emergence of resistance. Prompt follow-up of HCV RNA levels and assessment of therapy is necessary. All treatment, including peginterferon and ribavirin, should be discontinued if any of the following occur:

- While on boceprevir:
 - HCV RNA ≥ 100 IU/mL at week 12
 - HCV RNA detectable at week 24 or at any other timepoint thereafter
 - HCV RNA rebounds ($\geq 1 \log_{10}$ increase from the nadir HCV RNA) at any time while on treatment
- While on telaprevir:
 - HCV RNA is >1000 IU/mL at week 4 or 12
 - HCV RNA is detectable at week 24 or at any other timepoint thereafter
 - HCV RNA rebounds ($\geq 1 \log_{10}$ increase from the nadir HCV RNA) at any time while on treatment

Dosage, Administration, and Response Guided Therapy

Treatment duration with HCV protease inhibitor regimens are determined by virologic response at specific timepoints during treatment. For boceprevir, naïve patients who respond favorably with undetectable HCV RNA between weeks 8 and 24 may be eligible for shortened courses. Some treatment experienced patients may be eligible for shortened treatment durations if an undetectable HCV RNA is achieved by week 8. For telaprevir, treatment naïve patients with an undetectable HCV RNA between weeks 4 and 12 may be eligible for shortened courses.

Boceprevir or telaprevir should not be dose-reduced. If boceprevir or telaprevir is discontinued, it should not be restarted.

If ribavirin is stopped for ≥ 7 days or discontinued secondary to adverse event(s), then boceprevir or telaprevir should also be discontinued to avoid development of resistance.

Boceprevir Dosage and Administration

Weeks 1-4: peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) plus ribavirin (in 2 divided doses) with food: <75 kg: 1000 mg/day or ≥ 75 kg: 1200 mg/day; alternative weight-based ribavirin dosing: <65 kg: 800 mg/day, 65-85 kg: 1000 mg/day, >85 -105 kg: 1200 mg/day, >105 kg: 1400 mg/day.

Beginning at Week 5: Boceprevir 800 mg orally (4 x 200mg capsules) every 8 hours with food *plus* peginterferon *plus* ribavirin.

Boceprevir Response Guided Therapy is guided by on-treatment HCV RNA response and patient characteristics

Population	HCV RNA Assessment at Treatment Week ^a			Regimen	Total treatment duration
	Week 8	Week 12	Week 24		
Treatment Naïve (without cirrhosis)	Undetectable	Undetectable	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 24 weeks	28 weeks
	Detectable	Undetectable OR Detectable <100 IU/mL	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks, then PEG/riba for 12 weeks ^b	48 weeks
Treatment Naïve Poorly Interferon Responsive (defined as HCV RNA decline $<1.0 \log_{10}$ at week 4)	Undetectable OR Detectable	Undetectable OR Detectable <100 IU/mL	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 44 weeks	48 weeks
Prior Relapser^c/Partial Responder^d	Undetectable	Undetectable	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks	36 weeks
	Detectable	Undetectable OR Detectable <100 IU/mL	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks,	48 weeks

				then PEG/riba for 12weeks	
Prior Null Responder^e	Undetectable OR Detectable	Undetectable OR Detectable <100 IU/mL	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 44 weeks	48 weeks
Compensated Cirrhosis (Treatment-naïve or - experienced)	Undetectable OR Detectable	Undetectable OR Detectable <100 IU/mL	Undetectable	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 44 weeks	48 weeks
Treatment Futility	NA	If ≥100 IU/mL, discontinue all treatment	Detectable at Week 24 or at any timepoint thereafter; discontinue all treatment		

^aA sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10-15 IU/mL should be used for decision making to determine treatment duration with response guided therapy.

^b Discontinuation of boceprevir at week 36 is supported by modeling but was not directly studied in the clinical trials. Following a 4 week lead-in with PEG-RIBA, the addition of boceprevir to PEG-RIBA for 44 weeks achieved higher SVR compared to 24 weeks in late responders (detectable HCV RNA at week 8) in the registration trials.

^cRelapser=undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma;

^dPartial responder=decrease in HCV-RNA viral load greater than or equal to 2-log₁₀ by Week 12, but never achieved SVR;

^eNull Responder=decrease of <2 log₁₀ in HCV RNA after 12 weeks of prior HCV therapy with peginterferon and ribavirin; Boceprevir was not studied in null responders; this population was excluded from the Phase 2/3 study of patients who had previously failed treatment. Efficacy data and FDA labeling for this population is based solely on mathematical modeling

PEG=peginterferon; riba=ribavirin; NA=not applicable

Telaprevir Dosage and Administration

Telaprevir 750 mg orally (2 x 375mg tablets) every 8 hours with food (not low fat) for 12 weeks *plus* peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) and ribavirin (in 2 divided doses) with food: <75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day; alternative weight-based ribavirin dosing: <65 kg: 800 mg/day, 65-85 kg: 1000 mg/day, >85-105 kg: 1200 mg/day, >105 kg: 1400 mg/day.

Telaprevir must be administered with a high fat meal or snack containing at least 20 grams of fat. The high fat meal or snack should be ingested within 30 minutes prior to each telaprevir dose. Examples of some foods include a bagel with cream cheese, 0.5 cup nuts, 3 tablespoons peanut butter, 1 cup ice cream, 2 ounces American or cheddar cheese, 2 ounces potato chips, or 1.5 cup trail mix.

Telaprevir Response Guided Therapy is guided by on-treatment HCV RNA response and patient characteristics

Population	HCV RNA Assessment ^a			Regimen	Total treatment duration
	Week 4	Week 12	Week 24		
Treatment-naïve (without cirrhosis) OR Prior Relapser^b	Undetectable	Undetectable	Undetectable	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 12 weeks	24 weeks
	Detectable but ≤1000 IU/mL	Undetectable or Detectable but ≤1000 IU/mL	Undetectable	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks
Compensated Cirrhosis (Treatment- naïve or	Undetectable or detectable but	Undetectable or detectable but	Undetectable	Telaprevir plus PEG/riba for 12 weeks,	48 weeks

June 2011 Updated versions may be found at www.pbm.va.gov or <http://vawww.pbm.va.gov>

-experienced) OR Prior Partial Responder ^c OR Prior Null Responder ^d	≤1000 IU/mL	≤1000 IU/mL		then PEG/riba for an additional 36 weeks	
Treatment Futility	If >1000 IU/mL, discontinue all treatment	If >1000 IU/mL, discontinue all treatment	Detectable at Week 24 or at any timepoint thereafter; discontinue all treatment		

^aA sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10-15 IU/mL should be used for decision making to determine treatment duration with response guided therapy.

^bRelapser=undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma

^cPartial responder=decrease in HCV-RNA viral load greater than or equal to 2-log₁₀ by Week 12, but never achieved SVR

^dNull Responder=decrease of <2 log₁₀ in HCV viral load after 12 weeks of prior HCV therapy with peginterferon and ribavirin
PEG=peginterferon, riba=ribavirin

Management of Adverse Events

Despite the advances in efficacy, protease inhibitor therapy is not without its disadvantages. Adverse effects from both boceprevir and telaprevir did result in greater treatment discontinuation in a small number of patients compared to peginterferon/ribavirin. Telaprevir is associated with two key toxicities: skin reactions (rash and pruritus) and anemia, events were common, sometimes severe, and in some cases treatment-limiting. In December 2012, telaprevir's prescribing information was updated to include a boxed warning that fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with telaprevir combination treatment. Other events of interest include ano-rectal disorders and hyperuricemia. The two most common events reported with boceprevir include anemia and dysgeusia. Other events which occurred to a lesser extent include neutropenia and thrombocytopenia.

	Peginterferon alfa and ribavirin with boceprevir	Peginterferon alfa and ribavirin with telaprevir
Anemia	<p>The addition of boceprevir or telaprevir in combination with peginterferon alfa/ribavirin has been associated with an increased incidence of anemia. In clinical trials, the average additional decrease of hemoglobin was approximately 1-1.5 g/dL in boceprevir and telaprevir treated patients following recommended strategies for anemia management. Hgb levels may increase after boceprevir or telaprevir is discontinued; note that telaprevir is administered only for the first 12 weeks in combination with peginterferon alfa/ribavirin while boceprevir may be administered between 24 and 44 weeks in combination with peginterferon/ribavirin resulting in a potential longer duration of anemia.</p> <ul style="list-style-type: none"> Initial management of HCV treatment-related anemia should consist of ribavirin dose reduction to 600mg for hemoglobin <10g/dL (or as clinically indicated) Note that SVR rates in clinical trials were not compromised with ribavirin dose reductions to 600mg For additional monitoring and management of Hepatitis C treatment-related anemia, refer to the PBM CFU for Erythropoiesis Stimulating Agents. 	
Neutropenia	<p>In clinical trials, patients receiving boceprevir-containing regimens had higher rates of neutropenia compared to control while patients receiving telaprevir-containing regimens had similar rates of neutropenia compared to control. Treatment-related neutropenia was reported by 23% of all patients in the boceprevir treated patients and 18% in the peginterferon/ribavirin arms of the key studies. Coadministration of boceprevir with peginterferon alfa/ribavirin was associated with an increased incidence of Grade 4 neutropenia (ANC <500/mm³) compared to peginterferon alfa/ribavirin alone (7% and 4%, respectively) requiring more dose modifications and drug discontinuations. Granulocyte colony stimulation factor (G-CSF) use occurred in 9% of boceprevir treated and 6% of peginterferon/ribavirin treated subjects. Coadministration of boceprevir with peginterferon</p>	

	<p>resulted in a decrease in mean neutrophil counts, of approximately 1.5 to 2.8 x 10⁹/L. In several cases, neutropenia was associated with severe or life-threatening infections in the boceprevir-treated arms.</p> <ul style="list-style-type: none">Initial management of HCV treatment-related neutropenia (ANC <750/mm³) should consist of peginterferon alfa dose reduction (ie, peginterferon alfa-2a reduction from 180 mcg/week to 135mcg/week or peginterferon alfa-2b reduction from 1.5 mcg/kg/week to 1.0 mcg/kg/week)Refer to PBM CFU Filgrastim for Hepatitis C Treatment-related Neutropenia for recommendations for management of neutropenia																	
Thrombocytopenia	<p>For both boceprevir and telaprevir, the proportion of subjects experiencing thrombocytopenia (defined as platelet count <50 x 10⁹/L) was higher than that seen in patients treated with peginterferon alfa/ribavirin alone. For boceprevir treated patients, decreases in platelet count occurred within the first 12 weeks of treatment and then plateaued from week 12 to week 48. In clinical trials, patients with platelets less than 50 x 10⁹/L had peginterferon alfa dose reductions and those with platelets less than 25 x 10⁹/L had therapy discontinued.</p> <table><tr><th>Platelets (10⁹/L)</th><th>Peg/riba (n=547)</th><th>Boceprevir/Peg/riba (n=1548)</th><th>Peg/riba (n=764)</th><th>Telaprevir/Peg/riba (n=1346)</th></tr><tr><td>25 to <50</td><td>1%</td><td>3%</td><td rowspan="2">1%</td><td rowspan="2">3%</td></tr><tr><td><25</td><td>0</td><td><1%</td></tr></table> <p>In November 2012, eltrombopag, a thrombopoietin receptor agonist, received FDA approval for the indication of “treatment of thrombocytopenia in patients with chronic hepatitis C to allow for the initiation and maintenance of interferon-based therapy”. The approval was based upon efficacy and safety of eltrombopag in HCV patients being treated with only peginterferon/ribavirin; therefore, the efficacy and safety of eltrombopag in HCV patient being treated with boceprevir or telaprevir-containing regimens is unknown. In addition, eltrombopag has a boxed warning that it may cause hepatotoxicity and increase the risk of hepatic decompensation when used with interferon and ribavirin in patients with chronic hepatitis C. Eltrombopag also has a warning for thrombotic/thromboembolic complications; portal vein thrombosis has been reported in patients with chronic liver disease receiving eltrombopag.</p>					Platelets (10 ⁹ /L)	Peg/riba (n=547)	Boceprevir/Peg/riba (n=1548)	Peg/riba (n=764)	Telaprevir/Peg/riba (n=1346)	25 to <50	1%	3%	1%	3%	<25	0	<1%
Platelets (10 ⁹ /L)	Peg/riba (n=547)	Boceprevir/Peg/riba (n=1548)	Peg/riba (n=764)	Telaprevir/Peg/riba (n=1346)														
25 to <50	1%	3%	1%	3%														
<25	0	<1%																
Rash	<p>Overall, rash was reported with a similar incidence in boceprevir-containing treatment arms compared with peginterferon/ribavirin and was described as the typical rash observed with ribavirin use. There were no reported cases of Stevens-Johnson syndrome/toxic epidermal necrolysis.</p>		<p>Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with INCIVEK combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive telaprevir combination treatment after a serious skin reaction was identified. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, telaprevir, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.</p> <p>Patients with mild to moderate rashes should be followed for progression of rash or development of systemic symptoms. If rash progresses and becomes severe (i.e. rash</p>															

		<p>involving >50% of body surface area), telaprevir should be discontinued. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of telaprevir discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If medically indicated, earlier interruption or discontinuation of ribavirin and peginterferon alfa should be considered. Patients should be monitored until the rash has resolved. Telaprevir must not be reduced or restarted if discontinued due to rash. Treatment of rash with oral antihistamines and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. Treatment of rash with systemic corticosteroids is not recommended due to significant drug-interactions.</p> <p>The rash is typically eczematous, maculopapular, papular-lichenoid, and pruritic. The appearance and histopathology of the rash is comparable to the rash associated with peginterferon and ribavirin, although often is increased in severity and extent.</p> <p>In clinical trials, rash was reported in 56% of subjects who received telaprevir compared to 34% of peginterferon/ribavirin subjects. Rash most frequently began during the first 4 weeks, but could occur at any time during telaprevir containing regimen. Rash events led to discontinuation of telaprevir alone in 6% of subjects and discontinuation of telaprevir combination treatment in 1% of subjects. Severe rash (e.g., a generalized rash or rash with vesicles or bullae or ulcerations other than SJS) was reported in 4% of subjects who received telaprevir combination treatment compared to less than 1% who received peginterferon/ribavirin alone. The severe rash may have a prominent eczematous component.</p>
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Management of Drug interactions

It is very important to assess for drug-drug interactions before initiating therapy with an HCV PI and after the HCV PI is discontinued. Any dose modifications or medication changes that occurred prior to initiation with the HCV PI will need to be evaluated after the HCV PI is discontinued. Below is summary of role of CYP450 drug-drug interactions with boceprevir and telaprevir. Refer to prescribing information for more details.

Drug Interactions with Boceprevir and Telaprevir		
CYP450	Boceprevir is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5. Boceprevir is also a moderate inhibitor and substrate of P-glycoprotein. Drugs metabolized primarily by CYP3A4 may have increased exposure when administered with boceprevir, which could increase or prolong their therapeutic and adverse effects. Coadministration of boceprevir with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to boceprevir.	Telaprevir is a strong inhibitor of CYP3A4 and substrate of P-glycoprotein. Drugs metabolized primarily by CYP3A4 may have increased exposure when administered with telaprevir, which could increase or prolong their therapeutic and adverse effects. Coadministration of telaprevir with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to telaprevir.
Agents listed as Contraindications	<ul style="list-style-type: none"> • Alfuzosin • Rifampin • Dihydroergotamine, ergonovine, ergotamine, methylegonovine • Cisapride • St. John's Wort • Lovastatin, simvastatin • Pimozide • Sildenafil and tadalafil for treatment of pulmonary arterial hypertension • Orally administered midazolam, triazolam • Carbamazepine, phenobarbital, phenytoin • Drospirenone 	<ul style="list-style-type: none"> • Alfuzosin • Rifampin • Dihydroergotamine, ergonovine, ergotamine, methylegonovine • Cisapride • St. John's Wort • Atorvastatin, lovastatin, simvastatin • Pimozide • Sildenafil and tadalafil for treatment of pulmonary arterial hypertension • Orally administered midazolam, triazolam
Oral Contraceptive Therapy	<p>Pharmacokinetic studies of concomitant administration of oral HCV protease inhibitor and oral contraceptive therapy have shown decreased levels of oral contraceptives and therefore, oral contraceptives may be ineffective with concomitant administration of boceprevir.</p> <ul style="list-style-type: none"> • ↓ Ethinyl estradiol: use 2 other forms of contraception • Boceprevir: ↑ drospirenone: ↑risk of AEs 	
HIV Medications	<ul style="list-style-type: none"> • Please refer to Department of Health and Human Services "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" for a comprehensive review of pharmacokinetics and drug-drug interactions. • Per manufacturer, boceprevir is not recommended for concomitant use with any ritonavir-boosted protease inhibitor containing treatment regimen. • Potential for increased toxicity of the following: tenofovir • Potential for alteration in DAA activity and/or concomitant medications with the following: atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, efavirenz 	
Hepatitis B	Tenofovir: potential for increased tenofovir toxicity	
Immunosuppressants	<ul style="list-style-type: none"> • ↑↑ in immunosuppressant levels → significant dose reductions and prolongation of interval required • Potential for increased toxicity of the following: cyclosporine, sirolimus, tacrolimus, prednisone, methylprednisolone 	
Statins	<p>Potential for increased toxicity of the following: lovastatin, simvastatin, atorvastatin</p> <ul style="list-style-type: none"> • ↑ Risk of myopathy 	
PDE5 Inhibitors	<ul style="list-style-type: none"> • ↑ PDE-5 inhibitor levels (sildenafil, tadalafil, and vardenafil) • Dose adjustments required for ED 	

Quantity Limits and Refills

June 2011 Updated versions may be found at www.pbm.va.gov or <http://vawww.pbm.va.gov>

- Prescriptions should be limited to a 28-day supply. Refills should not be dispensed unless a clinical evaluation is performed by the provider. Adherence should be assessed prior to each renewal of prescription.
- Consideration should be given to dispensing 2 week supplies of medications to avoid excess waste if a patient fails to respond to treatment (as determined by required HCV RNA assessments and futility rules). Prompt assessment of HCV RNA levels and treatment response is necessary to avoid resistance and may require premature discontinuation of therapy.
- Boceprevir capsules should be refrigerated until dispensed. Once dispensed, capsules can be stored at room temperature up to 25°C (77°F) for 3 months. If stored in the refrigerator, boceprevir is stable until the expiration date printed on the label.
- Telaprevir capsules can be stored at room temperature between 59-86°F (15-30°C).

Cost of Hepatitis C Therapy

Cost of Boceprevir in combination with Pegylated interferon and Ribavirin for Chronic HCV

Population	Regimen	Total Treatment Duration	Cost of HCV Therapy^a
<i>Treatment Naïve (without cirrhosis)</i>	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 24 weeks	28 weeks	\$24,073
	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks, then PEG/riba for 12 weeks	48 weeks	\$34,124
<i>Treatment Naïve Poorly Interferon Responsive</i>	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 44 weeks	48 weeks	\$43,500
Prior Relapser/ Partial Responder	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks	36 weeks	\$31,844
	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 32 weeks then PEG/riba for 12 weeks	48 weeks	\$34,124
Null Responder or Compensated Cirrhotics (treatment-naïve or -experienced)	PEG/riba for 4 weeks, then boceprevir and PEG/riba for 44 weeks	48 weeks	\$43,500

^a Cost of Boceprevir and PEG/riba (at an average adult dose of \$190/week); FSS Pricing (May 2011)

Cost of Telaprevir in combination with Pegylated interferon and Ribavirin for Chronic HCV

Population	Regimen	Total treatment duration	Cost of HCV Therapy^a
Treatment-naïve without cirrhosis OR Prior Relapser	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 12 weeks	24 weeks	\$41,388
	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks	\$45,948
Compensated cirrhosis (treatment-naïve or -experienced) OR Prior Partial Responder OR	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks	\$45,948

^a Cost of Telaprevir and PEG/riba (at an average adult dose of \$190/week); FSS Pricing (May 2011)

Resources

- PBM Website includes Monographs and CFU for boceprevir and telaprevir; CFU for Management of Hepatitis C Treatment-related Anemia and Neutropenia
- VA Public Health Strategic Health Care Group Intranet Site <http://vaww.hepatitis.va.gov> includes tools for vaccination, screening for HIV, HCV, and HBV, and patient and provider education for hepatitis C therapy.
- VA HCRC and PHSBG HCV Treatment Recommendations, "Management and Treatment of Hepatitis C Viral Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office" are available at <http://vaww.hepatitis.va.gov>.
- PBM Clinical Pharmacy Practice Sharepoint
<http://vaww.infoshare.va.gov/sites/ClinicalPharmacy/default.aspx>
- National Hepatitis C Clinical Case Registry Reports which provide national, VISN, and station level data on relevant HCV care related topics: <http://vaww.hepatitis.va.gov/data-reports/ccr-index.asp>

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